A Case of Primary Aldosteronism With Discordant Hormonal and CT Findings

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Introduction of case

A non-smoking 46-year-old male was referred to our hypertension excellence center in Hopital Georges Pompidou in Paris because of hypertension associated with hypokalemia. He had a past medical history of asthma with inhaled corticosteroid therapy, corneal transplant and prostatic adenoma. He had neither diabetes nor lipid disorder. His BMI was 24.7kg/m². There was no family history of cardiovascular disease. Hypertension was diagnosed incidentally at the age of 43 years when he attended his doctor for a sport certification in 2011. His maximum systolic blood pressure was 190 mmHg and at that time he had a blood test that revealed hypokalemia, with the lowest potassium level being recorded as 3 mmol/L.

When first seen in the department, the patient was already treated with Amlodipine and Perindopril once a day. He also received corticoid inhalation for asthma and an alpha blocker (tamsulosine) for his prostate adenoma. The patient complained of headaches and dizziness. Diurnal ambulatory blood pressure measurement (ABPM) was very high; 167 /112 mmHg. Kalemia was 2.9 mmol/L with inappropriate urinary excretion of potassium (93 mmol/d). Fasting plasma glucose was 5.7mmol/l and LDL cholesterol was 3.88 mmol/l.

The patient was diagnosed with grade 3 hypertension and hypokalemia. Secondary causes of hypertension were explored and accordingly treatment was modified. Amlodipine and perindopril were stopped and Uradipil was prescribed. Despite oral potassium supplements of 9 g/day his kalemia remained at 3.0 mmol/L. Estimated glomerular filtration rate (eGFR) was 88 ml/min/1.73m² and urinary potassium excretion was still elevated (51 mmol/l). Renin and aldosterone levels were assessed in the seated position. Renin was 1.7 mUI/L and aldosterone concentration was 933 pmol/l (33.7 ng/dl) with an elevated aldosterone to renin ratio. The urinary aldosterone was also elevated (71 mmol/d) and a saline suppression test confirmed the diagnosis of primary aldosteronism with unsuppressed aldosterone secretion 426 pmol/l (15.7 ng/dl).

Dr. Laurence Amar: Looking at the target organ damage that was evaluated during this outpatient visit, left ventricular hypertrophy was suggested with the Cornell index and confirmed with echocardiography (LVMI = 121 g/m2.7 mass). He did not have microalbuminuria. Pulse wave velocity and carotid wall thickness were not performed. He had a CT scan. The slides show normal adrenals without any adenoma or hyperplasia (Figure 1).

There is a 46-year-old male with a history of hypertension for three years, associated with hypokalemia. We have a diagnosis of primary aldosteronism with normal adrenals. We know we could make another clinical pathological conference on the diagnosis of primary aldosteronism, but I think this is not the case today. Maybe we should discuss what we should do now that we agree that this patient has primary aldosteronism.

Prof. Rhian Touyz: This opens up the discussion to the audience. We have a very nice presentation of a young man with high aldosterone but normal adrenals. Does anybody have any suggestions?

Dr. Sharabi: In that case, the fact that he doesn't have an adenoma doesn't rule out a unilateral secreting hyperplasia. Plus, in many histological evaluations of adrenal glands, you see microscopic adenomas. So, if he can tolerate or responds to medical treatment, because of his age and the short disease duration, I will consider adrenal vein sampling to see if he has unilateral adrenal hyperplasia or secreting adenoma, despite the fact that in the CT scan you don't see anything. Because he is young and in his particular case, can be curated if indeed, unilateral adrenal lesion is found and resected.

Dr. Amar: I agree with you. We have 3 alternatives

1. I do not want or need to know if he has uni- or bilateral production of aldosterone.
2. I want or need to know if the secretion is uni- or bilateral.
3. I already know that it is bilateral.

So, your point is that we do not know if it is bilateral or not. If we want to know if it is uni- or bilateral, we move on to the next set of options.

Determining Unilateral versus Bilateral; Medical therapy or Surgery

The first option to consider is whether unilateral versus bilateral can be predicted without doing adrenal vein sampling. This was attempted by working on a prediction score for lateralized PA based on kalemia, eGFR and imaging results (1). However it could not be reproduced by other teams.

There are other options that have been published. The first one is metomidate PET(2), however, my unit does not have easy access to metomidate. The second option is measurement of 18 oxo cortisol(3). Now with liquid tandem mass spectrometry, it is possible to do some measurements in the blood that would help diagnose uni- versus bilateral overproduction of aldosterone.

The final option is adrenal vein sampling (AVS).

There are other possibilities. It could be considered that it is not necessary to know if this patient has uni- or bilateral disease. Maybe surgery would not be proposed to this patient because of comorbidities such as severe asthma in this patient. Or perhaps performing AVS in our centers

is not possible and it is complicated to address this patient somewhere else. Or maybe the patient does not want to know if he has uni or bilateral disease because he doesn't want to undergo surgery.

There are several options, although no specific answers. What would be the results of the surgery? What are the risks of AVS? What should we propose?

Option 1. MR antagonists could be tried. These drugs are known to work. There could be some adverse reactions to spironolactone but less for eplerenone. Looking at the literature, medical treatment has roughly equal success to surgical treatment(4)
Option 2. For this reason, medical treatment is a valuable therapeutic option.
Option 3. It appears the patient has two normal adrenals on the CT scan, therefore it must be bilateral and we need to address that.

Discussion continues

Dr. Amar: As Dr. Sharabi pointed out, sometimes there are nodules that we do not see on the CT scan. So, option 2 is not a good answer. Also, it has been reported that 48% of patients have normal adrenals on CT scan. A recent study reported that 32.6% of patients have lateralized production of aldosterone(5,6). Therefore, I would also say proceed to adrenal venous sampling.

Prof. Gian Paolo Rossi: I have no doubts that you should perform adrenal vein sampling in this patient. He is a young active man who had a medical examination in order to obtain a sports certificate, perhaps for a competitive sport activity. He needs to have the best chances of a long term definitive cure of his hypertension. If you can go back to your CT scan, I would like to make a point that in my experience is very important. Each hypertension specialist or endocrinologist should look themselves at the adrenal glands visualized with CT or MR. Here, on the left I do see a small enlargement (pseudo-nodule) at the confluence of the three leaflets, and a small lump but in the lateral leaflet, which cannot be disregarded by the Hypertensiologist because often aldosterone-producing adenoma are really tiny, e.g. less than 10 mm in maximum diameter. If the CT is not done with 2-3 mm-thick slices and one, who does not know the clinical case, does not look very carefully, even using the coronal reconstruction of the images, these tumors can easily be overlooked. I am really keen to see the histology if you operated on this patient.

Dr. Amar: I agree it is really complicated to know what is a normal adrenal gland. When we look at surgical cases, of course there is a bias in that only patients with more florid clinical phenoptypes get surgery. Do normal adrenals exist? All of us in our centers, have some "normal adrenals" which are usually taken from patients with kidney carcinoma and when we look at them, they may have some nodules. It is always difficult to differentiate between nodules that are linked to hormone secretion or are just physiological.

Dr. Emmanuelle Vidal-Petiot: Even if there was an obvious nodule, there is the opposite drawback and risk of thinking it is lateralized when it is not. In any case, we would go to adrenal vein sampling.

Dr. O. Steichen: You said that the perspective of the patient was important. This patient may not be willing to be operated. In your experience, what percentage of patients with normal adrenals refuse to undergo surgery (AVS)?

Dr. Amar: I think the proportion depends on the physicians who take care of the patients. Because it depends on what we say to the patient. When we honestly say, “there are two options, it is benign and will not necessarily worsen without surgery”, it is not the same as when we say “without surgery it will get worse”. Sometimes patients have the idea that drugs will not work that long. For patients of 46 years old, as in this case, maybe we are more likely to say “Okay, this patient should have surgery” than for a patient with exactly the same story but who is 65 or 70 years-old. Therefore, I think it is difficult to answer this question because it depends on what we say to the patient. It also happens that some patients cannot be recommended for surgery because of comorbidities. But I would say 15% of patients refuse to have surgery after an explanation of the risks and options. Most of the patients do accept.

Prof. Anna Dominiczak: I have a comment based on a real patient. You are absolutely right, it is very difficult at this stage. Although we all agree to the next step of your management, there are difficult patients. I remember one who still attends my clinic where we did sampling. It was lateralized and we operated. He agreed to have surgery. He was in his 50’s at the time. The patient was a local general practitioner, so a doctor himself. He wanted surgery and he had surgery. It was all successful. Blood pressure didn’t normalize and a few years later we realized there was also adenoma in the other adrenal that was also secreting. But at the time we did the sampling, there was an obvious lateralization.

Prof. Paulo Mulatero: I absolutely agree with you and also Professor Rossi. We should absolutely perform an AVS unless the patient refuses to have surgery. I think we can discuss about the CT scan or on the clinical criteria. We can have a high suspicion. We can have the doubt that there is probably something on the left adrenal, but, we should nevertheless, perform AVS. There is nothing reliable at the moment to suggest unilateral versus bilateral form. A paper has just been published in the last year about steroid profiling that could indicate the presence of an adenoma versus bilateral hyperplasia or even more specifically of a mutated adenoma or not(7). We could maybe, in the future, have stimulus to be more aggressive with performing the AVS, but at this particular moment we should perform an AVS on this man.

Dr. A-L. Faucon: I agree with you, AVS is recommended for this patient, because he is young and he seems to have severe hypertension. But my question is, generally, what are other criteria to perform AVS?

Dr. Amar: In the literature, AVS can be skipped in a patient with one single nodule who is younger than 35 years old(8). In the other cases, if the physician and the patient are willing to go to surgery we have to propose AVS.

Prof. Rossi: Actually, the decision not to perform AVS is based on the idea that presence of a tumor in a young person with a clear-cut biochemical picture of primary aldosteronism is already strong evidence for that node being an aldosterone-producing adenoma. This might be correct, but from the strictly logical standpoint, it does not make any sense. The two things are not related to one another. You can have a non-functioning adenoma in a 35-year-old person and a microadenoma contralaterally. At our institution, we do not do surgery without adrenal vein sampling. I think this is something that has to be said very clearly because otherwise we may remove the wrong adrenal harboring a non-functioning adenoma.

Dr. Amar: Yes, the point is that you are at an expert center with easy access to adrenal vein sampling. But if the patient is below 35 years old, the proportion of the discrepancies is very low between AVS and CT scan. Our unit also does it every time because it is easy for us, but when you have to refer your patients to another center it is more complicated. Jaap Deinum is leading a prospective randomised study to evaluate the diagnostic performances of AVS and CT scan. The results will be published by the end of 2016.

Dr. Neeraj Dhaun: My question is from a nephrology point of view. May I ask two questions relating to the hypokalemia? Was it symptomatic and did the patient's ECG show any suggestive changes?

Dr. Amar: No, there were no abnormalities on the ECG. In patients with primary aldosteronism we are dealing with chronic hypokalemia. Usually we do not see many complications in these patients.

Dr. Dhaun: Perhaps I missed this but while you were waiting to discuss AVS with the patient, did you treat him with a mineralocorticoid receptor antagonist?

Dr. Amar: No, because when we commence MR antagonists, then we have to wait six weeks to perform AVS. As long as we are in the exploratory phase of management of the patient, we prescribe amiloride. Amiloride has good effect on hypokalemia and it is easier for us in the preparation for AVS as it has to be stopped only 15 days before hormonal assessment.

Dr. T. Denolle: Do you want to try spironolactone or MR antagonist before surgery, even after AVS?

Dr. Amar: Yes, I would do it.

Adrenal Vein Sampling and Results

The standard operating procedure in our center is to perform AVS in the morning without interfering drugs (9). ACTH stimulation is not used. Two catheters are used: one for the right adrenal and one for the left adrenal, because anatomy is not the same for the adrenal veins and differently shaped catheters are necessary. Bilaterally simultaneous blood sampling is performed in our center, first right adrenal vein, then left adrenal vein, and femoral vein. There is a procedure for the management of the samples because any mistake on the management of the samples might lead to surgery on the wrong side. The patient signs a consent before the procedure. It contains everything that we discussed, including the indications and the risks.

Results of AVS sampling in this patient show that he has an elevated selectivity index (ratio of cortisol concentration between each adrenal vein and the femoral vein blood) on both the right and the left side (respectively 10.7 and 15.8). Looking at the lateralization index, there is 0.2 in the right adrenal and 3.6 in the left adrenal. Hence, this patient has a left lateralization of the production of aldosterone.

Dr. E. Vidal Petiot: Since you have a very large experience in adrenal veins, something I would be very interested to know is: what do you think about the different criteria to prove that you were indeed in the adrenal vein? Cortisol is usually what is used to prove that you were correctly placed, but I've read now that it is suggested to use metanephrine for instance. Or in our case, we have had samples where cortisol was not

elevated but aldosterone was. And so I always wonder it if is selective or not. Could you tell us what you think about that?

Dr. Amar: We have been using cortisol for years but, as you pointed, we now have data that show we may have other options. Several other hormones have been tested and this whole new field was opened by mass spectrometry. Several hormones have been shown to have a higher step-up between the adrenal vein and the peripheral blood than cortisol, as, for example, metanephrine, as you pointed out (10). Hence, use of these hormones can prove selectivity even when cortisol does not. The cut-off used for the selectivity index based on cortisol ranges from 1.10 to 3.00. ACTH would increase this ratio, thus enhancing the assessment of selectivity just because the levels of cortisol will be much higher. Regarding the discrepancies, you are correct, sometimes patients are judged to be non selective based on cortisol because the adrenal vein levels do not exceed those in the periphery, for example when there are aldosterone- and cortisol-co-secreting tumors. This underlies the need for other hormones as discussed previously. I think that within the years to come, we will have other solutions to interpret AVS. I think metanephrine is an interesting option

Dr. A. Tropeano: Do you always stop interfering drugs because your objective is to know if there is a lateralization?

Dr. Amar: Usually we try to stop interfering drugs. But the most important thing is to consider the renin levels at the time of AVS. Some centers do not stop interfering drugs but just check on the renin levels. If renin levels are low, the chances of secondary aldosteronism turning on aldosterone secretion in the unaffected (contralateral) adrenal gland are slim. We all avoid spironolactone, even though one paper entailing only four selected patients who underwent AVS under spironolactone, e.g. only 1.7% of the patients in the cohort, claimed that these patients did have an elevated lateralization index and had remission of primary aldosteronism after adrenalectomy(11). It is easier to perform AVS without interfering drugs. But if it is not possible, specifically in patients with very severe hypertension, then renin must be checked before performing AVS.

Prof. Rhian Touyz: You mentioned amiloride. What other drugs would you use as your drug of choice in patients with really severe hypertension?

Dr. Amar: For hypertension or for kalemia?

Prof. Touyz: For both as they are linked.

Dr. Amar: The patients with hyperkalemia need diuretics. During the work-up we avoid mineralocorticoid blockers and use classical diuretics. Amiloride is added to control hypokalemia.

Dr. Sharabi: Just a comment. Aliskiren would have been handy in this situation as it doesn't increase renin. But we don't have it anymore. I have a question. Is there a reason not to infuse ACTH during the adrenal vein sampling? In our experience, it does increase the selectivity index and it helps us in having clear results. We use ACTH infusion as part of the protocol.

Dr. Amar: With simultaneous procedures or sequential procedure?

Dr. Sharabi: Bilaterally simultaneous.

Dr. Amar: So the question is how do we interpret the data? There are several protocols, several cut-offs. And also the AVS is longer and it is more complicated for the radiologist.

Dr. Sharabi: Selectivity is enhanced as well as the aldosterone secretion.

Dr. Amar: So it increased the numbers but it doesn't change the fact that the radiologist or the cardiologist did catheterize the adrenal veins or not.

Dr. Sharabi: Just to complete the ACTH issue, the group from Australia have experience of 800 cases. They strongly advocate the use of ACTH. And as I said, in our small experience, not hundreds, it did help us in getting clear results. But I understand, having a slot of one hour in the radiology room, it is a hassle. So we start the ACTH infusion an hour in advance and then move them supine to the table in the invasive-radiology room to have the actual venous sampling. I recommend considering the use of ACTH infusion wherever it is feasible.

Dr. Amar: I think you have to use ACTH when you use sequential measurement. When you do simultaneous measurement it has never been proven to improve the results.

Dr. Dhaun: Could I ask you what the risks associated with AVS are in your center and how these vary between centers? Also, is there an increased risk of catheter-related thrombosis depending on the subsequent histology?

Dr. Amar: The expert of the complications of the AVS is present in this room. Prof. Paolo Mulatero collected all the cases that have been published. There were 24 cases of adrenal hemorrhage. It happened more often in the right adrenal(12). The training of the radiologist was not that different. Prof. Mulatero also performed the retrospective study among several centers which perform AVS. There were 2604 patients and there were only 16 adrenal vein ruptures. Can it happen? Yes it can happen. Does it happen often? No, it is very rare. However, a full discussion of possible risks and complications is essential before the AVS. Overall, it resolves with conservative treatment in 100% of the cases.

We do not see any difference with the histology that we get after. Histology is difficult because the classical pathological report would say "Conn adenoma". In fact what they see is an adenoma of the cortex. It is not possible to answer if it is secreting aldosterone without immunostaining, which in our center is not done routinely. Therefore, the answer to the question about the adenoma is usually not precise; pathologists are not that interested in it because it is benign.

Dr. Barigou: You evoked a selectivity index of 2.0. Supposing some cases we could not reach this selectivity index in both adrenal veins. In this situation, some studies suggested that we could interpret the adrenal venous sampling but we should reach a certain lateralization index compared to vena cava values (13). What do you think about that?

Dr. Amar: There is literature about the contralateral suppression index, which is the third index(13). The aldosterone to cortisol ratio in one adrenal vein is compared to the

peripheral vein. The idea is that if lower levels of aldosterone are measured in the adrenal vein than in the peripheral vein it would indicate that the contralateral adrenal has elevated production of aldosterone.

If it is not possible to have results of both adrenal veins, then if there is one adrenal vein that shows the production of aldosterone is suppressed, it could be inferred that the other vein is producing too much aldosterone. In this study it is shown that all patients with bilateral aldosterone hyperplasia are in the range between the lowest cut-off and the highest cut-off. Therefore, by looking at the suppression index, it is possible to find the patient with the overproduction of aldosterone(13).

It is also possible to have a suppression index that is low on both adrenal veins. The aldosterone to cortisol ratio is low in the right adrenal vein, low in the left adrenal vein, and it is higher in the peripheral vein. What do you do with those data? There is a definite need for more patients and more studies to be able to determine whether it is possible to decide on an adrenal venous sampling without having results of the other side.

Post AVS

Adrenal vein sampling was performed. The patient had left lateralization of the production of aldosterone. The case of this patient was discussed during a routine multidisciplinary meeting with the hypertensiologist, physiologist, radiologist, the surgeon and the geneticist.

A left adrenalectomy was proposed to the patient. It was performed laparoscopically. Before the adrenalectomy, the patient was treated with spironolactone and verapamil as all blood tests required for a diagnosis were complete and normal kalemia and controlled blood pressure were desired before surgery. It was also believed this course of action would result in less difficulty with hyperkalemia after surgery. There have been papers in the literature with mineralocorticoid insufficiency. Our center does not have such cases and this may be connected to the use spironolactone before surgery. Basically, when patients come to surgery, they have non-suppressed renin levels.

The day after surgery, the patient had a potassium level of 4.8 mmol/l. Six months after surgery, without any treatment since surgery, he has diurnal ABPM of 134/94 mmHg. He has improved blood pressure values, but he is not totally cured of hypertension. His kalemia was normalized. The hormone measurements show an unsuppressed renin and normal aldosterone to renin ratio. He was also given a saline suppression test and it showed that aldosterone was suppressed after the saline infusion. This patient has hormonal cure of his primary aldosteronism, but he still has hypertension, likely concomitant essential hypertension. Treatment was started with 300 mg per day Diltiazem.

The most recent follow up with the patient was a few days ago. The patient had ceased taking his tablets because he did not see a reason for drug therapy after having surgery for this. In the office, his blood pressure was 132/88 mmHg. He was asked to also complete ABPM or home blood pressure measurement, but those measurements have not been received yet. Kalemia was 4.6 mmol/L and he was basically well (Table 1).

Prof. Dominiczak: You stated there was a geneticist at your multidisciplinary meeting, but you didn't tell us what the geneticist added to the discussion. Clearly, there are

beautiful causative mutations in some of these patients that predict what happens clinically. There is a lot of work in your own center, trying, as we heard in the morning session, to use genetics to help predict the outcome of these patients. What was the geneticist's view?

Dr. Amar: The problem is there is a clinical routine for these patients. We know the somatic mutation only after surgery. For now, we cannot use it in the everyday routine for the decision of the management of the patient. What we usually do is propose a genetic test for all patients that have hypertension before the age of 30, which is not the case for this patient.

After surgery, if the patient agreed to be part to the ENSAT cohort, we collect all the tumors in the research lab to look for mutations. Actually, I still do not have the answer for this patient because they just took the tumors recently. I cannot tell you if he has a mutation or not, not yet.

Prof. Mulatero: I go back to the point of the ACTH stimulation or not. Simultaneous sampling is not a frequent procedure, already AVS is difficult. There are few radiologists that know how to do the simultaneous sampling. So there is a point for ACTH. In the two studies that have compared the performance of ACTH versus non-stimulated procedure in a large series, the result when you take into account a conservative ratio, are more or less the same. So at the end of the day, each center could decide the preferred strategy.

ACTH is indispensable if you don't do the procedure early in the morning, or, if for example the patient had an allergic reaction during the contrast for the CT scan and needs to be prepared with steroid treatment before the AVS. Another case is if the nodule is bigger and maybe co-secreting cortisol with aldosterone. This can confound the result, therefore, you want to be sure to stimulate the cortisol production in the other adrenal gland. Or you can use another normalization hormone such as metanephrine.

Dr. Amar: This patient had asthma as I said in the beginning. He was taking inhaled corticoid drug so we had this question. In fact, we consulted with his lung physician and stopped all the corticoids before doing the explorations. We checked that he still did not have corticotropin insufficiency.

Dr. Faucon: In this case, you stop the corticotherapy before the AVS. What do we have to do in practice with corticotherapy?

Dr. Amar: When patients take corticoids, there can be a corticotropin insufficiency, even if steriod is inhaled. Usually the habit is to lower the dose and then to check if there is corticotropin insufficiency.

Dr. Lorthioir: I understand that adrenal vein sampling must always be performed. Why do you perform the CT scan before doing AVS if you won't change your mind based on the CT data?

Dr. Amar: It is a good point. There are two answers. The first is 1% of the patients do have adrenal cortical cancer and for these patients we do not do AVS because they need surgery. The second is that a lot of radiologists use the CT scan to localize adrenal veins to be more accurate for the AVS.

In the German Conn's registry when viewing this retrospectively it was found to be very complicated to have good results on AVS procedures performed by radiologists in several centers(14). There were few patients (from 8% to 48%) that had bilateral selective cannulations at the German center. The radiologist or cardiologist was then trained and asked to view procedures in other more successful centers. Rapid cortisol assay was requested in order to provide cortisol levels during the procedures and they were asked to locate the adrenal vein. For these radiologists the success rate of the procedure increased.

Dr. Lorthioir: It is a little bit confusing as some people say that when you are screening for endocrine hypertension, you should perform a CT scan first and if you have normal adrenal glands, you should not do biological tests and change the treatments. It is sometimes difficult to give neutral treatments, so you confirm that there is no need to wait for the results of the CT scan to do biological test to confirm if there is hyperaldosteronism?

Dr. Amar: If there is hypertension and you are looking for endocrine causes of hypertension, you have to perform hormone assessment before doing a CT scan and not the opposite. This is recommended by all guidelines.

Dr Vidal Petiot: Physiologically it is indeed expected that ACTH will increase selectivity as it stimulates cortisol. We also have to keep in mind that acutely given ACTH stimulates aldosterone and we don't know to what extent it will stimulate more adenoma from physiologically secreted aldosterone and whether it will impact the interpretation of lateralization of the AVS.

This patient was lucky his eGFR was the same after his blood pressure dropped 50 mmHg. When we cure these patients, whether it is medically or surgically, we often reveal the underlying nephroangiosclerosis and eGFR drops a lot.

Dr. Amar: The patient is only 46 years old and he doesn't have any other vascular risk factors. I think that might be an explanation. But you are right, we often do reveal underlying pre-existing renal insufficiencies in these patients.

Dr. Dhaun: My first question is whether this patient had a classic dipping diurnal variation in blood pressure at diagnosis and whether this changed with treatment? And the second question relates to your choice of anti-hypertensive drug, verapamil. I was wondering why you chose verapamil as this is not a classic antihypertensive agent.

Dr. Amar: In patients with aldosterone overproduction, we sometime see a non-dipper profile on ABPM. Also, there are some patients with primary aldosteronism who have obstructive sleep apnea syndrome. When we look at the series of patients, the mean BMI among 500 patients is 27 or 30 kg/m² which is elevated. There are some physiopathological explanations that might explain the correlation between primary aldosterone and sleep apnea syndrome. This particular patient had a classical dipper profile and it remained the same after treatment.

We chose verapamil because we want non-interfering drugs during the workup of the patient. It has been shown that dihydropyridine increases renin, specifically, in the acute state. So when we change a drug, usually non-dihydropyridine drugs are used.

Dr. Dhaun: You wouldn't use an agent from another group, such as a non-calcium channel blocker antihypertensive?

Dr. Amar: When the exploration is ongoing, ACE inhibitor cannot be used, ARB cannot be used, diuretics cannot be used and MR antagonists cannot be used. Basically, the only thing left is alpha blockers and calcium channel blockers, or a combination of both. Verapamil is an excellent choice unless the patient has hypokalemia, in which case it can prolong the PQ interval and cause AV block.

Dr. Turc: Before the treatment, we sometimes use eplerenone which might be more selective than spironolactone.

Dr. Amar: Before surgery, we want to treat the patient. In France, we have an issue with eplerenone because it is not allowed to be prescribed for hypertension. It may only be used for cardiac insufficiency. Therefore, we usually prescribe low doses of spironolactone, for men it is 25 mg per day. If there is intolerance, then a switch to eplerenone is made. We begin with spironolactone to prove to our authorities that the recommended and less expensive drug was tried first.

Dr. Colussi: I have a question about another technique to check the laterality of the adenoma. There is a rapid improvement of imaging like the CT spector, for example, scintigraphy with radiolabelled cholesterol. Would it have a possible role as a substitute for AVS? Are there some studies, some data, about this new technique?

Dr. Amar: You are correct. There are new imaging techniques, for example using (11)C-metomidate positron emission tomography (PET)-CT. Maybe in a few years we will not need to do AVS anymore. But for now, in the clinical routine, it is the gold standard as most centers do not have access to a cyclotrone and thus to (11)C-metomidate synthesis.

Dr. Barigou: Do you perform a saline suppression test at the post-operative visit even if the renin was normal and the aldosterone was normal? Is this something that is recommended? And what is the rationale of that?

Dr. Amar: We first begin with renin and aldosterone levels and if the aldosterone to renin ratio is normal, it is not necessary to perform the saline suppression test.

Before surgery, the patients are usually willing to come back to the outpatient clinics for everything we ask of him. After surgery, particularly if they are cured, it is more difficult to have them back for follow-up testing.

Dr. Vidal Petiot: I just wanted to point out a paper from Laurence Amar's team that showed if you apply criteria from different places in the world to the same patient with the same procedure, you will have different clinical outcomes(15). We really need to move forward because 5-10% of patients with resistant hypertension have primary aldosteronism. Obviously, we really have an issue with interpreting this crucial procedure.

Dr. Amar: It is right that if we look at discrepancies between the interpretations on AVS in different centers, it is the same number as discrepancies between CT scan and AVS(15).

Dr. Marcus: In my center and I believe in my country [Portugal], we do not perform AVS sampling. You talked about other techniques to the diagnosis. Do you think the other techniques could potentially substitute the need for AVS?

Dr. Amar: Metomidate TEP is a very promising technique but for now it is complicated to prepare metomidate as this requires a very expensive cyclotrone facility on-site. If it is possible to have oxo-cortisol from blood tests, then hormonal assessments would be good.

A large European project ENSAT-HT is beginning now with the aim of using omics to diagnose PA and other endocrine hypertensions starting from just one blood sample. The project is in Horizon 2020, so maybe in 2020 we will have the answers.

Prof. Dominiczak: I would like to make one comment about metomidate. The center in Cambridge, Professor Brown, who we invited but could not come, is using it a lot with very good results. In the centers that can produce it close to the patient you might eventually replace adrenal vein sampling with this test. Prof. Brown was able to diagnose very small nodules and cure young people successfully. So I refer you to the studies published by Professor Morris Brown (JCEM 2012).

Dr. Sharabi: I am familiar with the recent literature about the genetics of aldosterone-producing adenomas. I don't know how to incorporate it into understanding the patient condition, diagnosis and treatment choices. Largely, these are somatic mutations.

Dr. Amar: In truth some, very rarely, are also germ-line mutations, albeit with different clinical phenotypes. But indeed for somatic mutations, we know the mutation(s) only after surgery (16). However, we are now trying to see if we can detect presence of somatic mutations before surgery by analyzing the blood from the adrenal vein sampling.

Prof. Dominiczak: Yes, we would need to rely on the cells present in the adrenal vein sampling or even maybe that is a dream. If we are very good at selecting it, cells that peripherally circulate and then do the DNA analysis of this. We are not yet there. But also the ability to compare phenotype and genotype. Once we have more large collections of patients, we can predict genotype based on phenotype and hormones and biology. That would be another way to go.

Conclusion

This case and the discussion illustrates the difficulties in managing patients with primary aldosteronism. Adrenal venous sampling is a key point for the diagnosis of lateralized primary aldosteronism. The randomized study on AVS mentioned earlier in this discussion has since been published. The study raises several new questions regarding: 1) the use of AVS as a gold standard, 2) the procedures of AVS, 3) the interpretations of AVS(17), and 4) opens the field for new multicentric prospective studies.

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Figure Legend

Figure 1: CT scan showing two normal adrenals

Table 1 : Characteristics of the patient before and after surgery

Characteristic	Before Surgery	After surgery (6 months)
Diurnal ABPM (mmHg)	167/112	138/94
Treatment score	2	0
Kalemia (mmol/l)	2.9	4.5
Unirnary potassium (mmol/d)	51	82
Renin (mUI/l)	1.7	17.2
Aldosterone (pmol/l)	933	245
Aldosteorne post Saline infusion test (pmol/l)	426	130